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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/716,166	11/17/2000	Douglas A. Treco	10278-014001	6951

26161 7590 07/12/2006

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EXAMINER	
JIANG, DONG	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 07/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/716,166	TRECO ET AL.	
	Examiner	Art Unit	
	Dong Jiang	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6,8-12,14,17,19,21-28,32-36,38-45,83,84,86,87 and 89-93* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 6, 8-12, 14, 17, 19, 21-28, 32-36, 38-45, 83, 84, 86, 87 and 89-93* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 November 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/18/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED OFFICE ACTION

The request filed on 18 April 2006 for a Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/716,166 is acceptable, and a RCE has been established. An action on the RCE follows.

Applicant's amendment filed on 18 April 2006 is acknowledged and entered. Following the amendment, claims 3-5, 13, 29-31, 37, 46, 85 and 88 are canceled, and claims 1, 6, 14, 17, 19, 38-41 and 84 are amended.

Currently, claims 1, 2, 6, 8-12, 14, 17, 19, 21-28, 32-36, 38-45, 83, 84, 86, 87 and 89-93 are pending and under consideration.

Withdrawal of Objections and Rejections:

All objections and rejections of claims 3-5, 13, 29-31, 37, 46, 85 and 88 are moot as the applicant has canceled the claims.

The prior art rejection of claims 1, 2, 6, 8-12, 90 and 91 under 35 U.S.C. 103(a) as being unpatentable over Sevarino et al. (Cell, 1989, 57(1): 11-19), in view of Stoller et al. (J. Cell Biol., 1989, 108: 1647-55, provided by applicants), Habener et al. (US 5,118,666), Suzuki et al. (US 5,891,671), and Patel et al. (CIBA Foundation Sumposium, 1995, 190: 26-50), is withdrawn in view of applicant's declaration.

The prior art rejection of claims 14, 17, 19, 21-28, 32-35, 38-45, 83, 84, 86, 87, 89, 92 and 93 under 35 U.S.C. 103(a) as being unpatentable over Sevarino et al. (Cell, 1989, 57(1): 11-19), and in view of Stoller et al. (J. Cell Biol., 1989, 108: 1647-55, provided by applicants), Habener et al. (US 5,118,666), Suzuki et al. (US 5,891,671), Patel et al. (CIBA Foundation Sumposium, 1995, 190: 26-50), and Warren et al. (Cell, 1984, 39(3 Pt2): 547-55), and Selden et al., US 6,531,124 B1, is withdrawn in view of applicant's declaration.

The prior art rejection of claim 36 under 35 U.S.C. 103(a) as being unpatentable over Sevarino et al. (Cell, 1989, 57(1): 11-19), in view of Stoller et al. (J. Cell Biol., 1989, 108: 1647-

55), Warren et al. (Cell, 1984, 39(3 Pt2): 547-55), and Nagai et al., US 6,010,883, is withdrawn in view of applicant's declaration.

Declaration

The declaration under 37 CFR 1.132 filed on 4/18/06 is sufficient to overcome the prior art rejections of claims 1, 2, 6, 8-12, 14, 17, 19, 21-28, 32-36, 38-45, 83, 84, 86, 87 and 89-93 based upon the Sevarino reference (Cell, 1989, 57(1): 11-19) for the following reasons:

In item 5 of the declaration, applicants provide a summary of experimental results, which indicates that various combination of pre and/or pro regions were tested for their ability to cause GLP-1 secretion, and they include: hGH signal peptide, factor IX prepro region and truncations thereof, SNV signal peptide, protein C signal peptide and truncations thereof, and IGF-1 prepro region. The results show that none of these constructs tested resulted in GLP-I secretion from fibroblasts, that in contrast to the results obtained with vectors containing GLP-1 with its own prepro region or any other pre and/or pro region tested, when the vectors containing nucleic acids encoding the prepro-region of somatostatin and GLP-1 were transfected into fibroblasts, GLP-1 was secreted in active form at significant levels. The art in general acknowledges that the prepro region of a secreted peptide would be useful for directing heterologous peptide secretion. The evidence by applicants that, with the exception of the prepro-region of the somatostatin, none of these constructs tested, including GLP-1's own naturally occurring prepro region, resulted in GLP-1 secretion from said fibroblasts is, therefore, unexpected. The prior art references applied would not have predicted such results generated using the specific construct and the specific cells. These results indicate that it is completely unpredictable whether a specific prepro-region of a secretory peptide would be able to direct peptide secretion in a specific type of cells. As such, each specific construct and cell type used for peptide secretion should be evaluated on its own merit based on evidence. Although the combined teachings of the cited art teach that the prepro-region of the somatostatin is useful in directing heterologous peptide secretion, none of them tested the specific combination of the construct and cells of the instant invention, i.e., the construct comprising a sequence encoding the prepro-region of a somatostatin and a sequence encoding a GLP-1, and the foreskin fibroblast cells. Therefore, the prior art rejections of the present claims are withdrawn.

Formal Matters:

Drawings

This application lacks formal drawings. The informal drawings filed in this application are acceptable for examination purposes. When the application is allowed, applicant will be required to submit new formal drawings.

Specification

The specification is objected to for the following informalities, appropriate correction is required for each item:

On page 5, lines 10-11, it is recited "but not more than 5, 10, 12, 12, 25, ...", wherein "12" is repeated twice. Such is seen throughout the entire disclosure, for example, on page 9, line 28, and page 15, line 13.

Rejections under 35 U.S.C. 112:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 14, 83, 84, 89 and their dependent claims 2, 6, 8-12, 17, 19, 21-28, 32-36, 38-45, 86, 87 and 90-93 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited in scope to a nucleic acid construct comprising a sequence encoding the prepro-region of a somatostatin and a sequence encoding a GLP-1; a fibroblast cell comprising said nucleic acid construct; and a method of making a GLP-1 by culturing said fibroblast, does *not* reasonably provide enablement for claims to a nucleic acid construct comprising a sequence encoding "a signal peptide" (claim 1, for example), a sequence encoding "a functional fragment" or "a variant" of the pro-region of a somatostatin with not more than 5-15 amino acid changes (claims 1, 83, 92 and 93, for example), and a sequence encoding a GLP-1 "analog" (claim 1, for example); any or all "non-endocrine cell" comprising said nucleic acid construct (claims 14, 21-25, 84 and 86, for example); or a method of making a

GLP-1 or analog thereof by culturing said "non-endocrine cell" (claims 38-40, for example). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The present claims encompass 1) a nucleic acid construct comprising a sequence encoding "a signal peptide" (claim 1, for example), a sequence encoding "a functional fragment" or "a variant" of the pro-region of a somatostatin with not more than 5-15 amino acid changes (claims 1, 83, 92 and 93, for example), and a sequence encoding a GLP-1 "analog" (claim 1, for example); 2) "non-endocrine cell" comprising said nucleic acid construct (claims 14, 21-25, 84 and 86, for example); or 3) a method of making a GLP-1 or analog thereof by culturing said "non-endocrine cell".

With respect to point 1), "a signal peptide" reads on any or all signal peptide; the variant of the pro-region of a somatostatin reads on a variant with less than 80% sequence homology to the referenced sequence (as there are 64 amino acids for the pro-region of the somatostatin); and a GLP-1 "analog" reads on any functional equivalent with or without sequence homology to GLP-1. However, as shown in the declaration, among several pre and pro regions tested including GLP-1's own naturally occurring pre pro region, with the exception of the prepro-region of a somatostatin, none of those constructs resulted in GLP-1 secretion from fibroblasts (item 5 of the declaration). These results clearly demonstrate that it is extremely unpredictable which signal peptide would resulted in GLP-1 secretion. In fact, the applicants came up with the same conclusion based on their own results as stated in the declaration that it is not clear why only the somatostatin prepro region, and none of the others tested could guide GLP-1 through the secretory pathway, and this result could not have been predicted from the prior art reference. Given the unpredictable nature of the prepro region for secretion, it would be even less predictable to choose "a functional fragment" or "a variant" of the pro-region of a somatostatin as that recited in the claims. Further, the specification does not disclose or test any functional

fragment or variant of the pro-region of a somatostatin, which would meet limitation of the claims, nor guidance or working example regarding same. As such, the specification does not reasonably provide enablement commensurate in scope with claims to a nucleic acid construct comprising a sequence encoding "a signal peptide", a sequence encoding a functional fragment or a variant of the pro-region of a somatostatin with "not more than 15 amino acid" changes, and it would require undue experimentation to practice the invention in a manner commensurate in scope with the claims. Therefore, only the prepro-region of a somatostatin, not the full scope of "a signal peptide" and "a functional fragment" or "a variant" of the pro-region of a somatostatin is enabled. With respect to an "analog" of GLP-1, the specification does not define the term, thus, given the broadest and reasonable interpretation, it reads on a functional equivalent with or without sequence homology to GLP-1. With the exception of several GLP-1 sequence variants (GLP-1(7-37), (GLP-1(7-36), and GLP-1-Gly8 (page 12, the second paragraph, for example), no other functional equivalents meeting the limitations of the claims were ever identified or particularly described in the specification. The specification fails to provide guidance or working examples of any functional equivalent of GLP-1, which may not share sequence homology, and would be within the limitations of the claims. Therefore, undue experimentation would be required of the skilled artisan to make the claimed invention in its full scope.

With respect to points 2) and 3), the term "non-endocrine cell" encompass any or all type of non-endocrine cells. However, only human foreskin fibroblast cells are tested and used for making GLP-1 peptide in the instant specification. Given the result disclosed in the declaration that GLP-1's own naturally occurring pre pro region does not result in GLP-1 secretion from the fibroblasts used, it strongly indicates that the cell type is critical for peptide secretion as GLP-1 is secreted from its naturally occurring endocrine cells. Once again, as indicated by applicants in the declaration, that it is not clear why only the somatostatin prepro region, and none of the others tested, including GLP-1's own naturally occurring pre pro region, could guide GLP-1 through the secretory pathway (in the foreskin fibroblast cells). Therefore, it is completely unpredictable which type of non-endocrine cells would be suitable for the claimed construct to make secreted GLP-1, and it would require undue experimentation to identify other non-endocrine cells having the desired property, and determine if such were suited to be used as claimed.

Due to the large quantity of experimentation necessary to identify "a signal peptide", [to generate a number of fragments and variants of the pro-region of a somatostatin recited in the claims and possibly screen same for secretory activity, and to identify "a non-endocrine cell", all of which would be suitable for GLP-1 secretion besides the pro-region of a somatostatin and foreskin fibroblast, and to generate non-sequence related functional GLP-1 "analog" as encompassed in the claims; the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex and extremely unpredictable nature of the invention, and the breadth of the claims which embrace a broad class of unrelated signal peptides, structural fragments and variants of the pro-region, and extremely diverse cell types, undue experimentation would be required of the skilled artisan to make the claimed invention in its full scope.

Conclusion:

No claim is allowed.

Advisory Information:

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 571-272-0872. The examiner can normally be reached on Monday - Friday from 9:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Dong Jiang, Ph.D.
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6/22/06

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